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Are tyrosine kinase inhibitors as effective as they are safe in renal cell cancer patients over the age of 65?

Efficacy of sunitinib in elderly patients with metastatic renal cell carcinoma

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Abstract
Aim: In the present study, we aimed to compare clinicopathological characteristics and survival results of young and elderly patients with renal cell cancer (RCC).
Material and Methods: Patients 65 years of age or older were classified into the elderly age group, while all others were classified into the younger age group. To determine the correlation between clinical and pathological parameters, the chi-square test or Fisher's exact test was used. The Kaplan–Meier method was utilized to analyze the survival rate.
Results: The median duration of follow-up was 24 (1.0-240.0) months. In young patients, the median survival was found to be 51.0 (95% CI 20.7-81.2) months, while it was 26.0 (95% CI 6.4-45.6) months in the group of elderly patients (p=0.03). The median progression-free survival (PFS) was calculated to be 25.0 months (95% CI 18.5-31.4) in young patients, while it was 8.0 (95% CI 4.6-11.3) months in elderly patients (p = 0.02). No significant difference was found between groups in terms of clinicopathological characteristics and data on treatment side effects (p <0.05).
Discussion: Although there is no significant difference between the two groups of ECC patients in terms of clinicopathological characteristics, overall survival may be shorter in the elderly patient group due to the age factor. However, in the elderly group, PFS was found to be lower despite the use of TKI, which suggests that these drugs are not as effective in elderly patients as in younger patients in spite of the ease of oral intake and a safe side effect profile. Further studies, which will be carried out with elderly patients, may clarify this issue.

Keywords
Renal Cell Cancer, Elderly Patients, Tyrosine Kinase Inhibitors

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Introduction

Renal cell cancer (RCC) is commonly a disease of elderly patients, and its incidence is strongly associated with age. According to SEER data, 49% of patients with RCC were reported to be 65 years of age or over [1]. By 2030, the majority of the population will be over 65 years of age, and hence a decrease can be expected in the incidence of metastatic RCC in elderly patients [2].

Since aging is a natural process when natural physiological reserves are depleted, vulnerability and impairment of homeostatic balance results in a more rapidly progressive pathological condition and leads to serious health problems [3,4]. The treatment process of elderly patients diagnosed with cancer is more complex than that of younger patients. It has been stated that causes of high mortality in elderly patients include high incidence, inadequate antineoplastic treatment, decrease in organ functions, insufficient treatment tolerance, reduction in stem cell reserve and repairability and underutilization of protective methods [5,6]. Decreased PFS and the presence of comorbidites in elderly patients have led to their underrepresentation in clinical studies. Therefore, suggestions on the treatment of elderly patients with mRCC are usually based upon the data obtained from young patients enrolled in these studies, which may not be optimal for elderly patients, as many elderly patients are fragile, have age-associated organ dysfunction and have more than one medical comorbidity [7,8].

Within the last decade, the median survival of mRCC has increased to over 36 months with the approval of more than ten targeted treatments and immune checkpoint inhibitors [9]. These advances in treatment have indicated that metastatic renal cells carcinoma is a disease with the potential of being chronic and can be cured with the simultaneous and sequential employment of agents, which have varying mechanisms of action and toxic effects. Yet, as elderly patients are underrepresented in clinical studies, there is still a paucity of information on the benefits and toxic effects of these drugs. Therefore, we have yet to understand how to reach treatment targets in elderly patients, and hence selections of treatments and their sequence create a particular challenge for clinicians.

Considering the growth in the elderly population all over the world, both the rate and the absolute number of patients having the disease will increase. Therefore, it is important to take into consideration the problems specific to the management of elderly patients. The aim of the present study was to analyze and evaluate the clinical characteristics, survival outcome, sunitinib treatment efficacy and toxicity data in young and elderly patients followed in our clinic.

Material and Methods

The present study retrospectively evaluated 100 patients followed and treated with the diagnosis of RCC in Medical Oncology clinic of Yıldırım Beyazıt University, Ankara Ataturk Training and Investigation Hospital between 2005-2014. The data of 100 patients included in the study were retrieved from patient files and recorded. The study was approved by the ethics committee of the Ankara Ataturk Training and Investigation Hospital.

Demographic characteristics of patients, presenting symptoms, ECOG performance status, smoking history, diseases, diagnostic method, histopathological characteristics and laboratory findings were recorded. Surgical treatment, cytokine treatment, tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib), other treatment modalities and survival outcomes were evaluated. The development of toxicity during treatment and dose alterations were recorded. Patients were staged according to the TNM criteria [10]. to Treatment response was assessed according to the RECIST (Response Evaluation Criteria in Solid Tumors) criteria, and side effects were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (Aes) version 4.0 (Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. May 28, 2009. Department of Health and Human Services; National Institutes of Health; National Cancer Institute. 2010; 14:3-4) [11]. Risk factors associated with shorter survival were evaluated according to the Memorial Sloan Kettering Cancer Center (MSKCC) risk classification [12].

Patients 65 years of age or older were classified into the elderly age group, while all others were classified into the younger age group. Overall survival (OS) was defined as the time from the date of diagnosis to death or final evaluation of the patient in the clinic. Disease-free survival (DFS) was defined as the time from the date of operation to the development of local recurrence or distant metastasis (months); and progression-free survival (PFS) was defined as the time from the onset of treatment to disease progression or development of distant metastases.

Statistical analysis

The data were analyzed with the SPSS 15.0 software program. Fisher and Chi-Square tests were used for nominal variables and numerical data. . The Kaplan–Meier method was utilized to assess survival rates, and comparisons were made with the log-rank test. Uni and multivariate analyses were performed with the Cox regression model. A p value <0.05 was considered statistically significant.

Results

Patient characteristics

The present study included 100 RCC patients with complete data. Patients were stratified into the young age group (≤65) and the elderly group (>65). The overall median age was 62 years (25.0-89.0), and 40% were over 65 years old. The median age was 71 years (66-89) in the elderly patient group, while it was 54 years (25-65) in the young patient group. The median follow-up period was 28.0 (2.0-240.0) months in young patients, while it was 20.5 (1.0-196.0) months in the elderly patient group.

The male/female ratio in patients was found to be 2.1. The number of patients at ECOG stage 0-1 was 87. The most common complaints at diagnosis were flank pain (31%) and hematuria (16%); 64.0 % of patients underwent radical nephrectomy, while 7% underwent partial nephrectomy. The number of patients diagnosed with biopsy was 28. In histopathological evaluation, 84 patients had clear cell and 16 patients had nonclear cell histology. The majority of the patients were at stage IV (55.0%). The most common sites of

distant metastases were lungs (34%), bones (28%), and liver (14%). Eleven patients underwent metastasectomy, of which, 4 patients underwent metastasectomy for lung metastasis, 3 for brain metastasis, 3 for surrenal gland metastasis and 1 for bone metastasis. According to the MSKCC criteria, 33 patients were in the favorable risk group, 36 in the medium and 31 in the unfavorable risk group.

Table 1. Characteristics of young (≤65 years old) and elderly (>65 years old) patients

Characteristics		≤65 n=60 (60.0 %) n (%)	>65 n=40 (40.0%) n (%)	p
Sex	Female	20 (33.3)	12 (30.0)	0.72
	Male	40 (66.7)	28 (70.0)	
ECOG	0-1	53 (93.0)	35 (87.2)	0.34
	2-3	4 (7.0)	5 (12.8)	
Smoking	Absent	18 (30.0)	17 (42.5)	0.36
	Present	18 (30.0)	8 (20.0)	
Accompanying Disease	Absent	19 (41.3)	13 (38.2)	0.78
	Present	27 (58.7)	21 (61.8)	
Surgical Procedure	Only biopsy	14 (25.5)	14 (37.8)	0.43
	Right nephrectomy	22 (40.0)	13 (35.1)	
	Left nephrectomy	19 (34.5)	10 (27.0)	
Pathology	Clear cell	51 (85.0)	33 (82.5)	0.74
	Non-clear cell	9 (15.0)	7 (17.5)	
Tumor Size	≤7.0 cm	20 (44.4)	11 (47.8)	0.79
	>7.0 cm	25 (55.6)	12 (52.2)	
Stage	I	10 (16.7)	4 (10.0)	0.18
	II	12 (20.0)	10 (25.0)	
	III	8 (13.3)	1 (2.5)	
	IV	30 (50.0)	25 (62.5)	
MSKCC Risk Classification	Favorable	23 (38.3)	10 (25.0)	0.32
	Medium	21 (35.0)	15 (37.5)	
	Unfavorable	16 (26.7)	15 (37.5)	
Anemia (at diagnosis Hgb <12 G/Dl)	Present	29 (61.7)	18 (51.4)	0.35
	Absent	18 (38.3)	17 (48.6)	
Neutrophilia (at diagnosis Neu>7.0x 10 9/L)	Present	11 (25.6)	10 (31.3)	0.59
	Absent	32 (74.4)	22 (68.8)	
Thrombocytosis (at diagnosis (Plt>400.000)	Present	11 (23.4)	3 (8.6)	0.07
	Absent	36 (76.6)	32 (91.4)	
Hypercalcemia (at diagnosis calcium >10.2 mg/dl)	Present	3 (7.3)	2 (6.1)	0.83
	Absent	38 (92.7)	31 (93.9)	
Hypoalbuminemia (Albumin <4 G/Dl)	Present	25 (62.5)	20 (69.0)	0.57
	Absent	15 (37.5)	9 (31.0)	
High creatinine (level at diagnosis creatinine >1.2 mg/dl)	Present	20 (42.6)	15 (42.9)	0.97
	Absent	27 (57.4)	20 (57.1)	
First line immunotherapy	IFN/IFN+IL	36 (60.0)	26 (65.0)	0.61
	Absent	24 (40.0)	14 (35.0)	
First line TKI	Sunitinib	29 (90.6)	14 (82.4)	0.36
	Pazopanib	2 (6.3)	3 (17.6)	
	Sorafenib	1 (3.1)	0 (0)	
Hypothyroidism during TKI treatment	Present	9 (34.6)	4 (25.0)	0.73
	Absent	17 (65.4)	12 (75.0)	
Any side effect during TKI treatment	Grade 1-2	12 (20.0)	6 (15.0)	0.79
	Grade 2-3	9 (15.0)	7 (17.5)	
	Absent	39 (65.0)	27 (67.5)	

ECOG: Eastern Cooperative Oncology Group, MSKCC: Memorial Sloan-Kettering Cancer Center, Other: Brain, surrenal gland, pancreas and peritoneum

No significant difference was found between the two patient groups with regard to clinicopathological characteristics, and hematological and biochemical parameters (P>0.05) (Table 1)

Treatment

Interferon treatment was given to 62 % of the patients. The number of patients receiving TKI after IFN was 49. Of these, 43 received sunitinib, 5 pazopanib and 1 sorafenib. Their mean age was 63 (27-78) years, with 67.4 % at the age of 65 or below. Patients taking sunitinib received a mean of 6.0 cures (1.0- 45.0) of treatment. During sunitinib treatment, the dose was reduced in 53.8% of patients and treatment was interrupted in 36.6%. The overall response rate was 68% and 53.8%, respectively in young and elderly patients, with no statistically significant difference (p=0.39).

Among side effects, hypothyroidism requiring treatment occurred in 30% of patients. Grade 3-4 toxicities included fatigue (34.9 %), anemia (27.9 %), rash on skin (16.3%), mucositis (18.8%), hand and foot syndrome (13.6%), neutropenia (7.0 %) and hypertension (4.6%). No significant difference was found between the two groups with regard to hypothyroidism (P=0.73) and other toxicities (P= 0.79) (Table 1). The rate of discontinuation of treatment due to adverse events was found to be similar in the two groups.

Survival

The median duration of follow-up was 24.0 months (1.0-240.0). During the follow-up period, 34 (56.7%) patients died in the young patients group, while 34 (85.0 %) patients died in the elderly group. The median overall survival was 51.0 (95% CI 20.7-81.2) months in the young patient group, while it was 26.0 (95% CI 6.4-45.6) months in the elderly group (p=0.03) (Figure 1). The median progression-free survival was 25.0 (95% CI 18.5-31.4) months in the former group, while it was 8.0 (95%

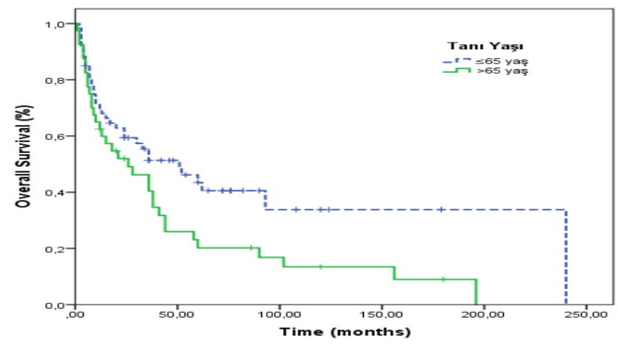

Figure 1. Overall survival of patients by age

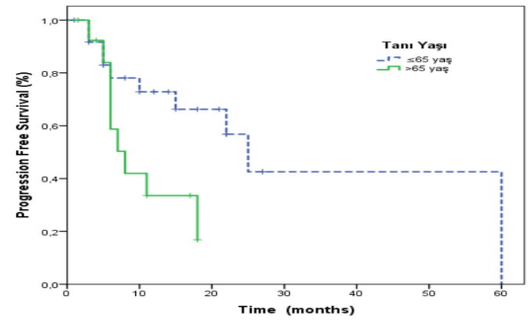

Figure 2. Progression-free survival of patients by age

CI 4.6-11.3) months in the latter group (p=0.02) (Figure 2).

In patients who received Sunitinib, the median GS was 30.0 months (95% CI 17.9-42.0), and the median PFS was 15 months (95% CI 3.4-26.6). During TKI use, disease progression occurred in 12 (44.4%) patients in the young patient group, and in 10 (66.7%) patients in the elderly patient group. In young patients using sunitinib, mean PFS was 16 (95% CI 4.4-28.6) months, while OS was 33.0 (95% CI 5.19-46.1) months. In elderly patients using Sunitinib, PFS was 7.0 (95% CI 4.1-9.8) months, while OS was 21.0 (95% CI 2.6-39.3) months. In patients who received Sunitinib according to the MSKCC (for sunitinib) criteria, in favorable, medium and unfavorable patients, median OS was respectively 102.0, 36.0 and 17.0 months (p<0.0001). In the above mentioned patients, median PFS was respectively 45.0 months (95% CI 1-99.3), 15.0 months (95% CI 1-33.9) and 6 months (95% CI 1.5-11.4) (p=0.05).

Discussion

In the present study, outcomes of an unselected patient population we followed in our daily practice were evaluated. In this retrospective study, it was established that improvement was obtained in survival in RCC carcinoma patients followed in a single center within a decade with the administration of TKIs following cytokine treatment. However, it was established that in elderly patients, OS and PFS were shorter than that in younger patients in spite of TKI treatment. In addition, no difference was found between the two groups in terms of toxicity patterns, which were tolerable in both.

The risk of toxicity and comorbidities are the most important factors in treatment selection in this elderly patient group. In the present study, in elderly individuals administered targeted treatment, treatment-associated toxicity, rates of serious toxicity, and therefore discontinuation of treatment were found to be similar to those in young patients. Likewise, in some previous studies, similar efficacy and tolerability rates were found in young and elderly patients [13,14]. In a metaanalysis, including six studies, the side effect profile was found to be comparable in young and old patients. However, side the effect profile was demonstrated to be higher than in earlier studies [13]. In a study performed with Japanese patients, the initial dose of sunitinib was maintained without cessation, and the importance of genetic alterations in sunitinib metabolism was emphasized [15]. In another Japanese study, the rate of treatment-associated toxicity, especially hematological one, was found to be very high in elderly patients, and accordingly, dose modification was carried out [16]. Maintaining adequate dose levels during the treatment process is the most important condition for treatment response [17,18]. The individualization of treatment in this manner may lead to marked changes in survival.

There are many additional factors influencing efficacy and toxicity in elderly patients; i.e. performance status, polypharmacy, nutrition, cognitive functions and socioeconomic status [19]. Various studies have indicated that immunological and genomic changes associated with aging may contribute to the pathogenesis of cancer and influence the efficacy of anti-cancer treatments [20]. These observations have revealed that some differences in the pharmacokinetics of anticancer treatment may partially contribute to the outcome of treatment.

In the present study, when the overall study population was considered, the median OS and PFS were found to be higher compared to previous clinical studies. Yet, in the elderly patient group, OS and PFS were found to be shorter in spite of TKI treatment. In some studies, it has been suggested that elderly patients may respond better to sunitinib treatment [21,22]. In a study on tumor biopsies in RCC, an age-associated difference has been demonstrated in tumor vascularity, and it was shown that patients with clear cell tumors ≥ 65 years of age had a higher microvascular tumor density compared to patients <65 years of age. In addition, the activity of angiogenic markers was found to be different as well. In order to explain this, it was proposed that patients with higher vessel microvascularity may respond better to treatment, or density of vessels may be inversely proportional to tumor aggressiveness [21,22].

It has been observed that the prognosis gets better consistently in elderly patients, and the number of patients receiving both first line and second-line treatment is increasing. Recently, in randomized controlled studies on patients using (immune checkpoint inhibitors, ICIs) inhibitors and combination regimens, their efficacy has been demonstrated [23,24].

We believe that our low number of patients and the fact that majority of these patients were in the medium and low-risk group may have contributed to these results. The difference in the results of clinical studies may be due to differences in patient selection and duration and dose intensity of sunitinib treatment. However, as the current study was retrospective, dose intensity and detailed drug interactions could not be evaluated. Comorbidities increasing with age, low-performance level, and multidrug combinations may create problems in management. In elderly patients with RCC, it is important to informpatients about drug efficacy and treatment tolerance.

Limitations of the present study include retrospective nature, small sample size, and inclusion of a heterogeneous population (stage, age, PFS, and metastatic site). Furthermore, it did not include immunotherapy-based therapies, which are currently standard treatments for mRCC, which is another limitation. The present study was carried out on a patient population followed in a single cancer treatment center, with homogenous treatment approaches and reference values for laboratory data, which may be considered a partial advantage. In addition, response evaluation was made with the same methods and similar approaches were used in side effect management, which is a further advantage.

In the near future, improvement in prognosis can be expected, especially with increased and longer-term use of ICI's. It may also be hoped that better-individualized treatment strategies may be developed for elderly patients by the determination of key molecules via gene sequencing apart from conventional predictive factors determining the efficacy of drugs and prognosis in association with comorbidities.

Our results may be significant as they may guide clinicians and help predict prognosis, and monitorize treatment toxicity. In conclusion, in elderly patients with mRCC, it is important to describe the clinical determinants of outcome. Therefore, inclusion of elderly patients in studies at a higher rate and reporting of results stratified by age is necessary.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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